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Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

The associations between fasting plasma glucose levels and mortality of COVID-19 in patients without diabetes

Yun Huang [a,1], Heming Guo [a,1], Yan Zhou [a,1], Jingjing Guo [a], Tiantian Wang [a], Xuming Zhao [b], Hui Li [c], Yihui Sun [d], Xuna Bian [e,*], Chen Fang [a,f,*]

[a] Department of Endocrinology, Second Affiliated Hospital of Soochow University, Suzhou, China
[b] Department of Emergency Medicine, Second Affiliated Hospital of Soochow University, Suzhou, China
[c] Department of Cardiology, Second Affiliated Hospital of Soochow University, Suzhou, China
[d] Department of General Surgery, Second Affiliated Hospital of Soochow University, Suzhou, China
[e] Division of Endocrinology, Department of Internal Medicine, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China
[f] Department of Nutrition, Second Affiliated Hospital of Soochow University, Suzhou, China

ARTICLE INFO

Article history:
Received 28 June 2020
Received in revised form
3 September 2020
Accepted 10 September 2020
Available online 16 September 2020

Keywords:
COVID-19
Plasma glucose
Mortality

ABSTRACT

Aims: Coronavirus disease 2019 (COVID-19) which is a novel pneumonia can rapidly progress to acute respiratory distress syndrome, septic shock, and multiple organ dysfunction syndrome. It has appeared in 196 countries around the world. We aimed to clarify the associations between fasting plasma glucose levels and mortality of COVID-19 in patients without diabetes.

Methods: We performed a retrospective, single-center study of 151 patients without diabetes in Tongji Hospital from January 1, 2020 to February 28, 2020. Past medical histories, clinical features and laboratory parameters were collected in these patients.

Results: Compared with survivors, non-survivors were more likely to have underlying medical conditions including hypertension and chronic pulmonary diseases. Non-survivors had higher C-reactive protein (CRP), procalcitonin (PCT), interleukin (IL)-2R, IL-6, IL-8 and, tumor necrosis factor-α (TNF-α) levels, while lower lymphocyte counts as compared with those of survivors (all $P<0.05$). Besides, patients with higher fasting plasma glucose (FPG) had higher IL-6, IL-8, CRP levels and mortality; while lower lymphocyte counts. After adjusting for age and gender, each tertile increment of FPG levels conferred 3.54-fold higher risks of death (odds ratio, 3.54; 95% confidential interval, 1.25-10.06, $P=0.018$).

Conclusions: Non-survivors combined with more comorbidities, more severe infection, and worse liver, kidney and cardiac function in patients without diabetes. Additionally, fasting plasma glucose levels were significantly associated with the risk of death in patients even with normal FPG and HbA1c levels.

* Corresponding authors at: Department of Endocrinology, Second Affiliated Hospital of Soochow University, 1055 Sanxiang Road, Suzhou 215000, China.
E-mail addresses: nkbxn@163.com (X. Bian), afa9911@sina.com (C. Fang).
[1] These authors contributed equally to this work.
https://doi.org/10.1016/j.diabres.2020.108448
0168-8227/

1. Introduction

A novel pneumonia of unknown cause was detected in Wuhan, China, which was later named as Corona Virus Disease 2019 (COVID-19) by the World Health Organization (WHO), and the virus that caused this epidemic was named as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [1].The outbreak of COVID-19 swept across China has aroused global concerns. Till May 5, 2020, more than 3.6 million COVID-19 cases have been confirmed around the world. According to different retrospective studies, among the patients with COVID-19, the mortality rate has huge variation [2,3]. However, severe cases were prone to suffer from various complications, especially death cases. Aged patients with underlying comorbidities including diabetes, hypertension, coronary heart disease are at increased risks to have poor prognosis. The clinical features of patients who have poor prognosis remain to be comprehensively studied which will be helpful to early indentify patients at high risk.

Recently, more and more studies highlighted the positive correlations between blood glucose levels and COVID-19 [4,5].COVID-19 patients with hyperglycemia have a crude mortality of about 7.3%, much higher than that of COVID-19 patients with normal blood glucose levels (0.9%) [6]. In diabetic patients, the percentage of patients who need intensive care was as high as 22.2% [7]. Besides, among the severe cases of death, 34% had hyperglycemia [8]. Thus, it is important to clarify the associations between blood glucose levels and mortality of COVID-19 in patients with or without diabetes. However, previous studies mostly focused on the management of blood glucose in patients with diabetes. Studies regarding the associations between fasting glucose levels and mortality of COVID-19 in patients with normal glucose regulation are sparse.

In this study, we aimed to describeclinical characteristic of patients without diabetes who were discharged or died of COVID-19 infection in two hospitals in Wuhan, China. We also evaluated the associations between fasting plasma glucose levels and mortality of COVID-19 in these patients.

2. Materials and methods

2.1. Study design and data collection

This retrospective study was carried out in Tongji Hospital. Diagnosis of COVID-19 was according to "Diagnosis and Treatment Scheme of New Coronavirus Infected Pneumonia" (trial version 6)" [9]. All cases had a history of exposure and most had clinical manifestations including fever or respiratory symptoms. The patients included in this study met the following criteria: (1) They were diagnosed new coronavirus infected pneumonia after examination of SARS-CoV-2 RNA by real-time polymerase chain reaction (RT-PCR). (2) They were admitted and treated in the Tongji Hospital from January 1, 2020 to February 28, 2020. (3) Patients had no history of diabetes and their glycosylated hemoglobin (HbA1c) levels less than 6.0% and fasting glucose levels (FPG) less than 6.1mmol/L. We screened 1024 hospitalized patients from the two hospitals. 151 patients who met the inclusion criteria were included into final analysis. The medical records of 151 patients were collected and examined by the research team from the two hospitals. Clinical, laboratory characteristics and outcomes data were acquired by the electronic medical record system.

2.2. Laboratory examination

Routine blood examinations were performed in all patients which included blood routine test, measurements of coagulation profile, HbA1c, FPG, serum urea nitrogen (BUN), creatinine (Cr), aspartate aminotransferase (AST), alanine aminotransferase (ALT), cardiac troponin I (CTnl), myoglobin, creatine kinase isoenzymes (CKMB), and brain natriuretic peptide (BNP) levels. Inflammatory markers which included C-reactive protein (CRP), procalcitonin (PCT), interleukin (IL)-1β, IL-2R, IL-6, IL-8, IL-10 and tumor necrosis factor-α (TNF-α) were also evaluated in each patients. SARS-CoV-2 was detected by RT-PCR method according to WHO interim guidance.

2.3. Statistical analysis

Analyses were performed using SAS version 9.3 (https://support.sas.com/documentation/-installcenter/93/index.html). Data were presented as median (interquartile ranges) for quantitative variables and number (percentages) for categorical variables. Kruskal-Wallis test or $\chi 2$ test were performed to compare differences among different groups. Logistic regression was used to assess the associations between mortality and fasting plasma glucose levels after adjustments for age and sex. Two-sided $p < 0.05$ was considered as representing statistical significance.

3. Results

A total of 151 cases with COVID-19 were admitted to the two centers, including 70 females and 81 males. By April 1, 15 of 151 cases died and their median duration from hospital admission to death was 11 days. 136 of 158 cases were discharged and their median duration from hospital admission to discharge was 22 days. We compared clinical and laboratory characteristics between survivors and deceased patients.

The results revealed that non-survivors were older than those survivors. The percentage of male patients was higher in non-survivors than that in survivors (P=0.0067). Compared with survivors, non-survivors were more likely to have underlying medical conditions including hypertension (60.0% vs. 28.7%, P=0.019) and chronic pulmonary diseases (40.0% vs. 7.4%, P=0.0015). Non-survivors had higher body temperature (36.9 vs. 36.5℃, P=0.014) and lower percutaneous oxygen saturation (SpO_2) (92%vs97%, P=0.010) than those in survivors at admission. As for biochemical parameters, FPG levels were found to be significantly higher in non-survivors as compared to those of survivors (5.86 vs. 5.03mmol/L, P=0.0003).

Meanwhile, non-survivors have higher AST (40 vs. 23 IU/L, P=0.0003), BUN (7.6 vs. 4.3mmol/L, P<0.0001), Cr (84 vs. 69umol/L, P=0.028) and eGFR (93 vs. 64ml/h·1.73m^2, P=0.0032) levels. CKMB, myoglobin and BNP were also found to be higher in deceased patients than those in survivors. As for inflammatory markers, non-survivors had significantly higher CRP (113.3vs 5.6 mg/L, P<0.0001), PCT (0.15vs 0.06 ng/ml, P<0.0001), IL-2R (1273 vs. 442U/ml, P<0.0001), IL-6 (97.0 vs. 3.2 pg/ml, P<0.0001), IL-8 (30.5 vs. 11.0 pg/ml, P<0.0001) and TNF-α (11.6 vs. 8.5 pg/ml, P=0.037); while significantly lower lymphocyte counts as compared to those of survivors (0.67 vs. 1.35×10^{12}/L, P<0.0001, Table 1).

Study population was further divided into three groups according to the tertile ranges of FPG levels. As shown in table 2, the mortalities were 1.92%, 6.12% and 22.0% in group 1, group 2 and group 3, respectively. Compared with that in group 1, the mortality in group 3 was remarkably higher (22.% vs. 1.92%, P<0.05). SpO2, IL-6, IL-8, CRP levels and lymphocyte counts differed significantly among three groups (all P<0.05). In comparison to those in group 1, IL-6, IL-8 and CRP levels were significantly higher; while lymphocyte counts were lower (all P<0.05). After adjusting for age and gender, each tertile increment of FPG levels conferred 3.54-fold higher risks of death (odds ratio, 3.54; 95% confidential interval, 1.25-10.06, P=0.018) (Table 2).

4. Discussion

In our study, all the patients with COVID-19 were elderly patients, and the median age was more than 60 years which indicated that older persons are more susceptible to COVID-19. The possible cause might be associated with a higher frequency of comorbidities [10]. Majority of patients in our study had several comorbidities. Our results also revealed that mortality was higher among patients with comorbidities. We found that there were 48 patients combined with hypertension, 17 patients with cardiovascular disease and cerebrovascular diseases. The proportions of hypertension, cardiovascular disease and cerebrovascular diseases were higher in non-survivors. The possible cause might be that these disorders share underlying pathophysiology related to the renin-angiotensin system (RAS). Activity of the angiotensin-converting enzyme 2 (ACE2) is dysregulated in cardiovascular disease, and this enzyme is used by SARS-CoV-2 to initiate the infection [11]. Besides, the patients with chronic pulmonary diseases also have higher mortality. It

Table 1 – The clinical characteristics between survivors and non-survivors.

	Survivors N = 136	Non-survivors N = 15	P values
Age (years)	61 (47–69)	75 (68–85)	<0.0001
Gender (Male/Female)	68/68	13/2	0.0067
Past medical history			
Hypertension (n, %)	39 (28.7)	9 (60.0)	0.019
Cardiovascular disease and cerebrovascular diseases (n, %)	13 (9.6)	4 (26.7)	0.069
Chronic pulmonary diseases (n, %)	10 (7.4)	6 (40.0)	0.0015
Chronic gastrointestinal and liver diseases (n, %)	8 (5.9)	0 (0)	1.0
Chronic kidney diseases (n, %)	2 (1.5)	1 (6.7)	0.27
Malignancy (n, %)	6 (4.4)	1 (6.7)	0.53
Body temperature (°C)	36.5 (36.2–36.9)	36.9 (36.5–38.0)	0.014
Percutaneous oxygen saturation (%)	97 (95–99)	92 (84–96)	0.01
Duration of hospital admission to discharge(days)	22 (16–30)	_	_
Duration of hospital admission to death (days)	_	11 (5–14)	_
Fasting plasma glucose (mmol/L)	5.03 (4.77–5.46)	5.86 (5.10–5.90)	0.0003
Aspartate aminotransferase (IU/L)	23 (18–34)	40 (32–59)	0.0002
Alanine aminotransferase (IU/L)	26 (15–40)	19 (11–39)	0.38
Blood urea nitrogen (mmol/L)	4.3 (3.3–5.5)	7.6 (6.4–9.5)	<0.0001
Creatinine (μmol/L)	69 (59–84)	84 (66–109)	0.028
Estimated glomerular filtration rate (ml/h·1.73 m^2)	93 (80–103)	64 (53–95)	0.0032
Creatine kinase isoenzyme (ng/ml)	0.6 (0.4–1.0)	2.6 (1.2–3.6)	<0.0001
Cardiac troponin I ≥ 1.9 pg/ml	5.3 (2.8–9.8)	35.3 (10.8–121.0)	<0.0001
Myoglobin (ng/ml)	34.4 (24.5–49.1)	198.2(128.2–318.6)	<0.0001
Brain natriuretic peptide (pg/ml)	76 (36–206)	697 (271–5735)	<0.0001
D-Dimer >21 μg/ml (n, %)	1 (0.78)	4 (26.7)	0.00037
C-reactive protein (mg/L)	5.6 (1.1–51.1)	113.3 (62.4–120.9)	<0.0001
Procalcitonin (ng/ml)	0.06 (0.05–0.10)	0.15 (0.14–0.29)	<0.0001
Interleukin-1β < 5.0 pg/ml (n, %)	84 (80.8)	12(85.7)	1.00
Interleukin-2R (U/ml)	442 (340–722)	1273 (884–1583)	<0.0001
Interleukin-6 (pg/ml)	3.2 (0.8–8.0)	97.0 (17.5–163.0)	<0.0001
Interleukin-8 (pg/ml)	11.0 (6.8–17.6)	30.5 (21.0–63.4)	<0.0001
Interleukin-10 < 2.5 pg/ml (n, %)	82 (78.9)	5 (35.7)	0.0016
Tumor necrosis factor-α(pg/ml)	8.5 (6.3–11.1)	11.6 (8.8–12.6)	0.037
White blood cells (×10^{12}/L)	6.18(4.84–7.51)	7.95 (5.49–9.90)	0.068
Lymphocyte (×1×10^{12}/L)	1.35 (0.91–1.86)	0.67 (0.43–0.97)	<0.0001

Table 2 – Clinical characteristics in patients with different levels of fasting plasma glucose.

Fasting plasma glucose	Group1 4.09–4.91 mmol/L	Group2 4.91–5.38 mmol/L	Group3 5.38–6.09 mmol/L	P value
Age (years)	60 (43–67)	64 (50–71)	63 (51–71)	0.36
Gender(Male/Female)	26/26	26/23	29/21	0.42
Body temperature (°C)	36.5 (36.3–36.9)	36.5 (36.1–36.9)	36.6 (36.3–37.3)	0.058
Percutaneous oxygen saturation (%)	98 (96–99)	96 (93–98)*	97 (93–98)	0.032
Interleukin-1β < 5.0 pg /ml (n, %)	35 (85.4)	34 (85.0)	27 (73.0)	0.17
Interleukin-2R (pg/ml)	392 (306–576)	365 (252–578)	560 (420–912)	0.056
Interleukin-6 (pg/ml)	2.8 (0.8–6.3)	4.9 (1.6–13.10)	6.9 (2.0–26.5)*	0.031
Interleukin-8 (pg/ml)	11.0 (6.5–14.2)	10.9 (7.0–20.0)	18.1 (9.6–25.6)*	0.012
Interleukin-10β < 5.0 pg/ml (n, %)	31 (75.6)	31 (77.5)	25 (67.6)	0.43
White blood cells ($\times 10^{12}$/L)	6.14 (4.83–7.19)	6.13 (4.70–7.99)	6.45(5.38–8.19)	0.39
Lymphocyte ($\times 10^{12}$/L)	1.44 (1.02–2.04)	1.14 (0.90–1.80)	1.10(0.66–1.61)*	0.049
C-reactive protein (mg/L)	2.9 (1.0–28.9)	15.05(0.95–62.65)	35.6 (2.1–89.7)*	0.028
Procalcitonin (ng/ml)	0.06 (0.05–0.085)	0.06 (0.05–0.14)	0.10(0.06–0.17)	0.13
Mortality (n, %)	1 (1.92)	3 (6.12)	11 (22.0)*	0.0007

* indicated P<0.05 as compared with group 1

may be explained that patients with poor pulmonary function are more likely to progress to respiratory failure under the attack of COVID-19.

In addition, our results demonstrated that non-survivors had more severe complications including acute cardiac injury, acute kidney injury, shock and secondary infections. Increasing attention has been paid to these complications during hospitalization. Besides, we found that AST levels were strongly associated with the risk of death which was consistent with previous studies. Previous studies also revealed that the increase of AST was more frequent than that of ALT in severe patients upon admission [7,12]. Recently, Lei F's study confirmed that elevated liver injury indicators, especially AST, were strongly associated with the mortality risk according to the results from 5771 adult patients with COVID-19 pneumonia. It indicated that liver injury indicators should be monitored during hospitalization.

Previous studies analyzed clinical characteristics of the patients with diabetes which revealed that the poorly controlled FPG levels could worsen the outcome of the new coronavirus disease [13]. In a retrospective study of 2041 patients with COVID-19, the results revealed that elevation of blood glucose level predicted worse outcomes in hospitalized patients with COVID-19 [14]. Another study indicated that tight glycemic control could improve clinical outcomes in patients with diabetes [15]. The underlying mechanism of the close relationship between hyperglycemia and SARS-CoV-2 might be due to the fact that ACE2 receptors also express on β cells; therefore, the virus could coulf directly attack the pancreas. It may render infected COVID-19 patients more prone to develop hyperglycemia [16].

Our study analyzed the influence of fasting blood glucose on the prognosis of patients without diabetes. Non-survivors reported higher FPG level compared with survivors. Further analysis revealed that inflammatory parameters including IL-6, IL-8 and CRP were higher in the patients with higher FPG. Meanwhile, the counts of lymphocytes were lower in the highest FPG group compared to other two groups. These data indicated that elevating FPG levels were associated with infection and immunity in COVID-19 patients without diabetes. The underlying mechanism remains to be elucidated. It might be associated with impaired innate immunity, adaptive immunity and altered metabolisms according to the previous studies [17,18]. Recent study reveal that elevated glucose levels directly induce viral replication and proinflammatory cytokine expression. It may also make T cell infected by virus more easily. The viral infections could increase the expression of programmed cell death protein 1 (PD-1) by T cells. This might explain why elevated glucose levels during CoV-2 infection may lead to T cell dysfunction and lymphopenia [19]. Our study indicated that patients with higher FPG levels also have higher mortality, even in patients without diabetes, FPG is still a risk factor of death.

There are several limitations in our study. This study was retrospective, and some data of cases were incomplete due to relatively insufficient medical resources, which may lead to bias. Data were collected from two centers, so the sample size was relatively limited. Although obesity is linked to an increased risk of COVID-19 [20], detailed data on body mass index of the patients with COVID-19 are lacking in this study, because we could not acquire the weight and height of all patients involved in our study. Finally, we examined the association between COVID-19 and FPG, but we cannot demonstrate causality.

5. Conclusions

In conclusion, in comparison to survivors, non-survivors combined with more comorbidities, more severe infection, and worse liver, kidney and cardiac function. In addition, fasting plasma glucose levels were significantly associated with the risk of death in patients even with normal FPG and HbA1c levels.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

The work was supported by the Science and Technology Project of Suzhou (grant numbers SYS2019070). The study funder was not involved in the design of the study; the collection, analysis, and interpretation of data; writing the article; and did not impose any restrictions regarding the publication of the article.

Ethics approval

All procedures performed involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Author's Contributions

CF and XNB contributed to the study conception and design. Material preparation and data collection were performed by YZ, JJG and TTW. The data analysis were performed by YH and HMG. The first draft of the manuscript was written and revised by YH, HMG and YZ. YHS, HL, and XMZ commented on previous versions of the manuscript and reviewed the manuscript. All authors read and approved the final manuscript.

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